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CRITICAL REVIEW AND INVITED COMMENTARY

## Effect of neurostimulation on cognition and mood in refractory epilepsy

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### SUMMARY



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Epilepsy is a common, debilitating neurological disorder characterized by recurrent seizures. Mood disorders and cognitive deficits are common comorbidities in epilepsy that, like seizures, profoundly influence quality of life and can be difficult to treat. For patients with refractory epilepsy who are not candidates for resection, neurostimulation, the electrical modulation of epileptogenic brain tissue, is an emerging treatment alternative. Several forms of neurostimulation are currently available, and therapy selection hinges on relative efficacy for seizure control and amelioration of neuropsychiatric comorbidities. Here, we review the current evidence for how invasive and non-invasive neurostimulation therapies affect mood and cognition in persons with epilepsy. Invasive therapies include vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). Noninvasive therapies include trigeminal nerve stimulation (TNS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS). Overall, current evidence supports stable cognition and mood with all neurostimulation therapies, although there is some evidence that cognition and mood may improve with invasive forms of neurostimulation. More research is required to optimize the effects of neurostimulation for improvements in cognition and mood.

**KEY WORDS:** Vagus nerve stimulation, Deep brain stimulation, Responsive neurostimulation, Trigeminal nerve stimulation, Repetitive transcranial magnetic stimulation, Transcranial direct current stimulation, Epilepsy surgery.

Epilepsy—the enduring tendency for recurrent, unprovoked seizures—is a debilitating disorder that affects millions of patients worldwide.<sup>1,2</sup> Despite the availability of more than 20 anticonvulsant medications, seizures are incompletely controlled by medication in a third of cases.<sup>3–5</sup> If seizures are well-localized in the brain, resection of the

epileptogenic focus can result in high rates of seizure freedom.<sup>6,7</sup> However, some patients are not candidates for resection, typically because they have multiple seizure foci or a focus co-localizing with eloquent cortex. For these patients, an alternative treatment is neurostimulation, which includes vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS), as well as recent, less-invasive therapies including trigeminal nerve stimulation (TNS), transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS). These therapies vary in their efficacy for seizure reduction<sup>8</sup> and are associated with different side-effect profiles.<sup>9</sup>

Of increasing interest is how these neurostimulation therapies affect mood and cognition (egg, memory, attention, language, and executive function) because both are well-recognized comorbidities of epilepsy. Depression may be a stronger predictor of quality of life than seizure frequency in patients with in epilepsy.<sup>10,11</sup> Here, we summarize the current evidence on the effects of neurostimulation on

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## KEY POINTS

- Mood disorders and cognitive deficits are common comorbidities in epilepsy that profoundly influence quality of life
- Several forms of neurostimulation are available, and selection hinges on seizure control and amelioration of neuropsychiatric comorbidities
- We review the evidence for how invasive and noninvasive neurostimulation therapies affect mood and cognition in persons with epilepsy
- Overall, current evidence supports stable cognition and mood with all neurostimulation therapies, but more research is necessary

cognition and mood, and how it should be used to guide treatment strategy to optimize patient outcomes.

## METHODS

Three separate queries of PubMed were made to find relevant articles. Searches were restricted to English-language studies with human subjects. The search terms were the following: “epilepsy,” with “cognition,” or “mood,” and “vagus nerve stimulation,” “RNS,” or “deep brain stimulation.” This led to 6 separate queries in total (eg, “epilepsy cognition vagus nerve stimulation,” “epilepsy mood vagus nerve stimulation,” and so on). The references of relevant studies and reviews were evaluated for additional articles. Studies were included for the following reasons: (1) the article was peer-reviewed; (2) there was a form of neuromodulation intervention; (3) original data on either cognition or mood were presented; (4) the primary indication for neuromodulation was intractable epilepsy; and (5) the sample size was larger than 5 patients or subjects to minimize potential publication bias. Studies were excluded if they were determined to have overlapping patients from other studies or were meeting abstracts only.

Level of evidence was determined based on past recommendations.<sup>12</sup> Level 1 evidence was considered either a randomized, controlled trial or a properly controlled experimental study. Level 2 consisted of experimental studies with fewer than 20 subjects, prospective observational or case-control studies. Level 3 evidence was provided by retrospective studies.

## RESULTS

Queries for studies investigating cognition returned 46, 28, and 3 for vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation (or RNS), respectively. The queries for mood returned 88, 22, 4 for vagus nerve stimulation, deep brain stimulation, and responsive

neurostimulation (or RNS), respectively. The included studies are summarized in Tables 2 and 3.

## DISCUSSION

### Vagus nerve stimulation

VNS is a widely used and well-investigated form of neurostimulation for epilepsy. A coil electrode is positioned around the left vagus nerve in the neck and connected to a pulse generator implanted in the chest. The precise mechanism of action is unclear. One hypothesis is that VNS sends antidromic pulses to the brainstem nucleus of the solitary tract and nucleus locus coeruleus, which in turn activate noradrenergic neurons that project diffusely in the brain to reduce seizure frequency, cortical spread, and duration.<sup>13</sup> The results of a double-blinded randomized study (EO5) consisting of 195 patients described median seizure reduction of 45% at 1 year, with 35% of patients being responders (ie, over 50% seizure reduction) and 20% having a seizure reduction of over 75% (Table 1).<sup>14</sup>

Like other forms of neurostimulation, VNS tends to have progressively increasing efficacy, meaning that longer duration of treatment correlates with better seizure control. For example, a study of 28 patients reported a change from a median 28% seizure reduction at 1 year to 72% reduction at last follow-up, which was 5–7 years.<sup>15</sup> Common side effects are typically minor and include throat irritation, cough, dysphonia, and sleep disruption.<sup>16,17</sup>

### VNS effects on cognition

The overall effect of VNS on cognition is unclear, and much of the investigation has focused on memory. However, there is some evidence that VNS increases cognitive functioning, at least in the short term (Table 2). Clark et al.<sup>18</sup> showed that when patients read unfamiliar, emotionally neutral paragraphs, they were more likely to retain tested, highlighted words if they were stimulated with 30 s of 0.50 mA pulses after reading the text. The authors concluded that VNS enhanced word retention and thus short-term memory. Important study limitations were the sample size (only 10 patients) and that the results were relatively short term.

Another study of 20 subjects investigating the effects of VNS on attention, cognition, and emotional reactivity found that subjects had improved working memory performance with VNS.<sup>19</sup> More specifically, patients were presented with a triangle pointed upward or downward and had to recall its orientation when prompted by a visual cue. Patients had significantly reduced recall errors when cyclic VNS was on than when it was off (odds ratio [OR] 0.63). In contrast, Helmstaedter et al.<sup>20</sup> tested verbal and figural recognition ~10 months after VNS implantation and found that stimulation negatively affected aspects of cognition. In their study, 11 patients were subjected to high-intensity VNS (over 1 mA) during and immediately following verbal and figural

**Table 1. Responder rate frequency (ie, percentage of patients with  $\geq 50\%$  seizure reduction) for invasive neurostimulation from open-label randomized controlled trials**

	Vagus nerve stimulation	Deep brain stimulation	Responsive neurostimulation
1-Year seizure reduction	45% (n = 195)	41% (n = 99)	44% (n = 182)
1-Year responder rate	34% (n = 195)	43% (n = 105)	44% (n = 182)
2-Year seizure reduction	47% (n = 188)	56% (n = 82)	53% (n = 175)
2-Year responder rate	43% (n = unclear)	N/A	55% (n = 175)
5-Year seizure reduction	64% (n = 90)*	69% (n = 59)	66% (n = 172)
5-Year responder rate	64% (n = 90)*	68% (n = 83)	61% (n = 172)

Declining number data were used when available. Medians are provided unless otherwise specified. <sup>13,36,49,66,67</sup>  
<sup>\*</sup>From retrospective, open-label study (Kuba et al 2009).<sup>68</sup>

recognition tasks. The subjects were initially exposed to novel word lists and figures before being tested on recognition. The subjects performed significantly worse during figure recognition with VNS stimulation than without it, whereas performance was unchanged in verbal recognition. The authors suggest that their results and conclusions differed from those of Clark et al.<sup>18</sup> because (1) the patients were stimulated during learning as well as immediate recognition, whereas Clark et al. only delivered stimulation during retention intervals, and (2) the stimulation was stronger in their experiment compared to Clark et al. ( $>1$  mA vs 0.5 mA). Limitations of this study include a small sample size (n = 11) and the fact that the control group was described as healthy, implying that they were not patients with pharmacoresistant epilepsy.

Longer-term studies have generally shown that VNS has no significant effect on memory.<sup>21</sup> A randomized, controlled study of 160 patients investigated the long-term cognitive effects by testing patients prior to implantation and then 3–4 months postoperatively.<sup>22</sup> One group of patients was assigned to minimal VNS stimulation, whereas another was assigned to the clinically used stimulation intensity. There was no significant difference between the 2 groups for any of the testing metrics, and the authors concluded that there were no cognitive changes. In another study of 40 patients investigating the long-term effects of VNS on cognition, patients were scored immediately before and 6 months after VNS implantation using abstract reasoning multiple choice tests.<sup>23</sup> There was no significant difference between the exams, suggesting that VNS has no long-term effects on cognition, at least for that domain. Smaller studies with longer testing intervals (eg, 12 months) have shown similar results.<sup>24,25</sup>

The positive cognitive effects from VNS, if they exist, are likely seen beyond 1-year postimplantation. Data in pediatric patients suggest that VNS may have positive effects on aspects of cognition outside of memory. Orosz et al<sup>26</sup> investigated the effects of VNS on 347 pediatric patients, assessing different qualities like alertness, concentration, memory, verbal communication, and progression with school work, as well as frequency of seizure reduction at 12 and 24 months. The results showed that a

relatively high proportion of patients substantially improved in concentration, verbal communication, and progress in school work between 12 and 24 months, with about half of patients showing no improvement in memory. Specifically, the number of patients who were “better or much better than before VNS” in concentration were 85/200 (42.5%) and 60/109 (55.0%) at 12 and 24 months, respectively, 57/200 (28.5%) and 45/109 (41.3%) at 12 and 24 months for verbal communication, and 62/200 (31%) and 37/109 (33.9%) at 12 and 24 months for progress with schoolwork. This suggests that VNS could have a positive effect on long-term cognition but that the benefit may not be realized until after 12 months. A limitation of this study was that there seemed to be patients lost to follow-up at 12 and 24 months, which allowed for potential selection bias. Furthermore, an analysis of provider survey data of 5,000 patients, including 3,000 with over 1-year follow-up, showed that patients had improvements in alertness, verbal communication, and memory.<sup>27</sup> The authors note that their data could have been skewed toward more favorable outcomes because physicians have a natural desire to see improvement in their patients; therefore the results must be interpreted within that context. Another limitation is that these studies are retrospective and thus cannot control for reduction in seizure frequency as a potential confounding factor. Taken together, the literature does not support cognitive impairment with chronic VNS and there are limited data to suggest that it may enhance cognition in certain areas, particularly over long periods.

### VNS effect on mood

The use of VNS in patients with refractory epilepsy has generally shown an improvement of mood (Table 3). VNS has been explored as a treatment for a number of psychiatric disorders (eg, depression, obsessive compulsive disorder, and mood disorders).<sup>28</sup> In particular, VNS has been shown to be effective in patients with treatment-resistant depression (TRD), as assessed by the Inventory of Depressive Symptomatology–Clinician Administered Version (IDS-C),<sup>29</sup> and TRD is an US Food and Drug Administration (FDA)–approved indication for VNS. However, the positive

Table 2. Summary of studies investigating cognition in VNS, DBS, and RNS

Study	Subjects	Classification	Evidence level	Methods	Findings
Vagus nerve stimulation Borghetti et al (2007)	12	Experimental study	2	Subjects underwent Mismatch Negativity (MMN) wave testing (an indirect assessment of preattentive cognitive processes) prior to VNS implantation (baseline), 4-6 months post-operatively with 0.25 mA VNS stimulation, and then after the subsequent 4-6 months with 0.5 mA VNS stimulation	MMN latencies and amplitude did not change significantly among the baseline or follow-up measures, implying there was no difference in cognition
Clark et al (1999)	10	Double-blind, randomized, controlled trial	1	Subjects were stimulated after reading unfamiliar paragraphs with highlighted words and were asked to recognize the words after VNS or sham stimulation	VNS stimulation after reading test paragraphs significantly increased word recognition performance
Dodrill & Morris (2001)	160	Double-blind, randomized, controlled trial	1	Subjects were tested with multiple cognitive tests before VNS implantation and 12-16 weeks post-operatively	There were no significant differences between preoperative and postoperative cognitive scores
Englot et al (2017)	5,000	Retrospective registry data analysis	3	Data obtained from VNS Therapy Patient Outcome Registry was analyzed for quality of life and cognitive metrics	Physicians reported subjective improvements in alertness, verbal communication, school/professional achievements, and memory at last follow-up
Ghacibeh et al (2006)	10	Experimental study	2	Patients with VNS implantation were tested while VNS was turned on versus off using the Hopkins Verbal Learning Test, which assesses learning and memory	VNS had no impact on learning but did positively influence retention and consolidation
Helmstaedter et al (2001)	11	Experimental study	2	Subjects were tested on recognition of novel words and figures after prior exposure with and without simultaneous VNS stimulation	Patients performed significantly poorer with VNS stimulation with figure recognition. There was no difference in performance for verbal recognition
Hoppe et al (2001)	36	Single-arm follow-up study	2	Subjects were tested at baseline (ie, 1-month preoperative) and at least 6 months postoperatively with multiple neuropsychological outcome tests	The were no significant differences between preoperative or postoperative cognitive scores, which included attention, memory, language, and executive functions
Klinkenberg et al (2012)	40	Prospective, longitudinal, observational cohort study	2	Subjects were tested with Raven Standard Progressive Matrices at baseline and 6 after VNS stimulation	There were no significant differences between the baseline and 6 months after VNS stimulation cognitive scores
McGlone et al (2008)	16	Prospective, case control study	2	Subjects were tested with multiple cognitive tests at baseline preoperatively and 12 months following VNS implantation	There were no significant differences for any metrics between the baseline and follow-up test periods
Miatton et al (2011)	10	Prospective case series	2	Patients with amygdalohypocampal DBS were evaluated preoperatively and 6 months postoperatively with multiple intelligence quotient (IQ) scales and immediate or delayed recall	The results were mixed, with positive improvement on various tests with negative or no improvement on others
Orosz et al (2014)			3		

Continued

Table 2. Continued.

Study	Subjects	Classification	Evidence level	Methods	Findings
	200 at 1 year; 109 at 2 years	Retrospective multicenter study		Clinicians assessed multiple metrics of cognition in their patients at 1 and 2 years after VNS implantations	Roughly one third of patients were subjectively improved in concentration, verbal communication, and progress in school work between 1 and 2 years. About half of patients were unchanged in terms of memory
Sun et al (2017)	20	Experimental study	1	Subjects were tasked with recalling the orientation of a triangle pointed up or down after being prompted by a visual cue	Cyclic VNS stimulation produced lower odds of errors in recalling triangle orientation (OR 0.63, 95% CI 0.47–0.85)
Tsai et al (2016)	37	Prospective, multicenter, open-label clinical study	2	The intelligence quotients (IQ) of pediatric patients were assessed preoperatively and at 12 months postoperatively	There was no significant difference in preoperative and postoperative IQs
Deep brain stimulation Hartikainen et al (2014)	12	Experimental study	2	Patients were tested with reaction-based tests while DBS was alternated between on and off every 5–6 min at 140 Hz	The findings were that DBS had direct effect that resulted poorer response inhibition but better attention allocation
Oh et al (2012)	9	Clinical trial	2	Patients were assessed preoperatively and at least 1-year follow-up. IQs and cognitive variables were tested by various scales and tests	Most cognitive scores did not significantly change between baseline and follow-up. Delayed verbal memory mean scores improved significantly by 68%. Word fluency test mean scores improve significant by 70%–80%
Salanova et al (2015)	103	Prospective randomized clinical trial	1	DBS patients were tested at baseline prior to surgery and 1–5 years postoperatively with various neuropsychological tests	There were significant improvements at 5 years in attention, executive function, and subjective cognitive function with statistically insignificant positive trends in verbal and visual memory scores. There was an insignificant negative trend for expressive language
Troster et al (2017)	66	Retrospective analysis of prospective randomized, clinical trial	3	DBS patients were tested at baseline prior to surgery and 7 years postoperatively with various neuropsychological tests	There were no declines in cognition for any objective metric used. Three of 4 means for executive function metrics improved significantly by 15%–40%
Responsive neurostimulation Loring et al (2015)	191	Double-blind, randomized, controlled trial	1	Subjects were tested with neuropsychological measures at baseline prior to implantation and 1 or 2 years postoperatively. The tests used included Boston Naming Test (BNT) and Rey Auditory Verbal Learning Test (AVLT)	There were no significant declines in cognitive function: 23.5% of patients improved in BNT scores; 6.9% and 6.8% of patients improved in AVLT learning and delayed recall scores, respectively

OR, odds ratio; CI, confidence interval.<sup>18,20,22–27,37,38,43,52,69–74</sup>



Table 3. Summary of studies investigating mood in VNS, DBS, and RNS<sup>23,30–33,37,38,53,75–77</sup>

Study	Subjects	Classification	Evidence level	Methods	Findings
Vagus nerve stimulation Elger et al (2000)	11	Multicenter randomized, controlled trial	I	Subject mood data were collected 4 weeks before VNS implantation (ie, baseline) and 3 and 6 months postoperative follow-up. Mood was assessed with standardized mood rating scales and subscales, and self-reported questionnaires	There was a significant improvement in most of the scores for the mood rating scales and subscales, as well as self-reported questionnaires. Mean subscale depression scores decreased by 37.7%. Mean subscale for a combined depression/anxiety subscale decreased by 18.2%
Hallbook et al (2005)	15	Prospective case series	2	Patients were assessed using a visual analogue scale for mood and a depression self-rating scale preoperative as well as 3 and 9 months postoperatively	There was a mild improvement, as 73.3% and 33.3% of patients reported improvement in mood and depression, respectively
Harden et al (2000)	40	Case-control study	2	Mood was assessed at baseline and 3 months following VNS implantation via clinical assessment and self-reported questionnaires	There was a significant decrease roughly 20%–30% in scores across 3 of 4 mood metrics between baseline and 3-month follow-up, indicating that patient mood improved
Hoppe et al (2001)	28	Post-hoc retrospective analysis	3	Subjects filled out self-report questionnaires that investigated mood and quality of life measures 4 weeks prior to implantation and at follow-up, which was at least 6 months post-operatively. The tests were Befindlichkeits-Skala (BFS) for dysphoria, Beck Depression Inventory (BDI) for depressive symptoms, and Self-rating on Anxiety Scale (SAS) for anxiety	The patients scored significantly lower in the BFS (–24.7%) and SAS (–12.8%), implying that patients had lower levels of dysphoria and anxiety at follow up. There was no significant difference in BDI, implying there were no differences in depression
Klinkenberg et al (2012)	33	Prospective, longitudinal, observational cohort study	2	Subjects were tested at baseline and 6 after VNS stimulation with Profile of Mood States (POMS), which scored multiple mood states like tension, anxiety, and depression	The POMS mean scores significantly decreased in terms of tension (–25.2%), depression (–35.5%), and anxiety (–34.4%) between baseline and after 6 months of VNS stimulation, indicating mood improvements
Ryvlin et al (2014)	112	Randomized, controlled trial	I	Patients were randomized to VNS and best medical practice (BMP) or BMP alone. Subjects were tested with a number of depression metrics at 1 year, eg, the Centre for Epidemiologic Studies Depression Scale (CES-D) and Neurological Disorders Depression Inventory in Epilepsy Scale (NDDI-E)	There were no significant differences between the treatment and control groups in terms of baseline changes in CES-D and NDDI-E scores at 1 year
Deep brain stimulation Salanova et al (2015)	103	Prospective randomized clinical trial	I	DBS patients were tested at baseline prior to surgery and 1–5 years postoperatively with various mood tests, which were synthesized into one composite t-score for different domains (eg, depression, anxiety)	There was a significant increase in composite T-scores from for depression, tension/anxiety, and total mood disturbance from baseline to 5-year follow-up
Sun et al (2015)	6	Experimental study	2	Patients were tested with a computer-based reaction time test with emotional distractors while DBS cycled every 5–6 min among either ATN or control thalamic stimulation, or off stimulation	A higher frequency electric stimulation of the ATN was associated with higher attention paid toward emotional stimuli, though stimulation was not cyclic like in typical therapeutic use

Continued

Table 3. Continued.

Study	Subjects	Classification	Evidence level	Methods	Findings
Troster et al (2017)	66	Retrospective analysis of prospective randomized clinical trial (Level 3 evidence)	3	Authors reanalyzed data from the SANTE trial. DBS patients were tested at baseline prior to surgery and 7 years postoperatively with various mood tests	There were no significant changes for depression, apathy, or anxiety scores between baseline and 7-year follow-up
Responsive neurostimulation Meador et al (2015)	191	Double-blind, randomized, controlled trial	I	Mood surveys were administered at baseline prior to surgery and 1 and 2 years postoperatively. Surveys included were the Beck Depression Inventory-II (BDI-II) and Profile of Mood States (POMS)	BDI-II mean scores significantly improved by 15.2% and 17.9% after year 1 and 2, respectively. POMS mean scores improved by 17% and 20.8% after year 1 and 2, but only the improvement after year 2 was statistically significant

effect of VNS on mood in patients with refractory epilepsy is less clear. A study that analyzed self-report questionnaires from 28 VNS patients with refractory epilepsy found that, although VNS made patients less tense and dysphoric (as measured with by 2 self-reported scales designed to assess anxiety and dysphoria), there were no improvements in any metrics of depression as measured by the Beck Depression Inventory, a self-reported questionnaire.<sup>30</sup> A larger study of 112 patients undergoing VNS therapy found improvement in quality of life but no significant improvement in metrics that measure depression.<sup>31</sup> Conversely, Klinkenberg et al<sup>23</sup> reported a prospective longitudinal observational cohort study of 41 patients with refractory epilepsy treated with VNS, and found that patients had lower levels of anxiety, tension, and depression at 6-month follow-up. A number of smaller studies also found that VNS was associated with reduction in depressive symptoms.<sup>32,33</sup> Overall, the current evidence is mixed but generally supports a positive effect of VNS on mood.

### Deep brain stimulation

DBS was originally shown to be effective in movement disorders, like Parkinson's disease and essential tremor, and it has since been utilized in other neurological disorders, including refractory epilepsy.<sup>34</sup> Although the exact mechanism of action for treating seizures is unclear, it is thought that electrical stimulation of key brain regions creates a pseudo-lesion that disrupts seizure propagation.<sup>34</sup> Targets of stimulation include the centromedian and anterior nuclei of the thalamus, due to their roles in cortical activation and the circuit of Papez, respectively. Velasco et al.<sup>35</sup> investigated the effect of stimulating the centromedian nucleus for treating generalized seizures in 13 patients with Lennox-Gastaut syndrome and found that the overall seizure reduction was 80% at 18 months. Similarly, Son et al<sup>36</sup> found that centromedian thalamic nuclei stimulation effectively reduced seizures in 11 of 14 patients, including 100% of those with Lennox-Gastaut syndrome.

Recently, the anterior thalamic nucleus (ATN) has emerged as a promising target for DBS in epilepsy. Salanova et al.<sup>37</sup> reported the results of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) study, a prospective randomized blinded trial of 110 patients treated with bilateral ATN stimulation. Median seizure frequency reduction for ATN DBS was 41% and 69% at 1 and 5 years, respectively, whereas the responder rate (percent of patients with at least 50% seizure reduction compared to baseline) was 43% and 58% at 1 and 5 years, respectively (Table 1). Potential limitations of DBS of the ATN pertain to patient subjective reports of memory problems and depression, although there is no evidence of objective, long-term neurobehavioral worsening.<sup>38</sup> There is evidence of sleep disruption related to thalamic stimulation,<sup>39</sup> which could conceivably explain memory and mood symptoms. Other complications reported in the SANTE trial included



pain associated with the procedure, implant site infection, and misplaced leads.

### DBS effects on cognition

Much of the data on the cognitive effects of DBS come from studies of patients undergoing ATN stimulation (Table 2). DBS may be effective in treating disorders of memory and cognition, like Alzheimer's and Parkinson's disease,<sup>40</sup> and so DBS for epilepsy may be associated with cognitive benefits as well.

There is relatively recent evidence that DBS of the medial temporal lobe in various neurological disorders has the potential to enhance learning and memory.<sup>41</sup> The ATN is intricately involved in learning and memory, and it may also play a role in executive function.<sup>42</sup> Thus it would seem intuitive that any effect of stimulation on the ATN would effect cognition, specifically memory. Results from a small study of 9 patients with at least 1-year follow-up showed that cognitive testing improved significantly after DBS of the ATN in verbal fluency tasks and delayed verbal memory.<sup>43</sup> Specifically, patients improved in their "category" and "letter" word fluency tasks as well as on delayed verbal recall tasks; moreover, none of the patients showed any significant declines in the cognitive metrics used.

There was concern for memory and cognitive decline with long-term treatment with ATN DBS. New-onset memory problems were endorsed by almost 30% of patients in the SANTE trial, although 50% of them had memory impairment at baseline.<sup>37</sup> However, objective metrics from the SANTE trial showed that patients had significant improvements in attention and executive function without significant declines in verbal or visual memory at 5 years. A later study reanalyzed the data from the SANTE trial to investigate the complaints of memory deficits and depression and found that these patients did not have any objective cognitive declines through the blinded or open-label phases.<sup>38</sup> Moreover, the patients actually improved significantly in some tested components of executive function, visual spatial memory, and attention. Executive function and visual attention were tested via the Delis-Kaplan Executive Function System (D-KEFS), whereas visual spatial memory was tested via the Brief Visual Memory Test-Revised. The mean scores for 3 of 4 metrics testing executive functioning in D-KEFS improved significantly roughly 15%-40% between baseline and follow-up. Two mean scores for visual attention metrics improved approximately 20% in that time, and the mean for 1 visual spatial metric improved about 8%. There were important limitations of this study that should be considered. First, although there were no negative cognitive effects, there was no long-term control group with which to compare results. Therefore, the authors argue that patients should still be monitored for changes in cognition. Second, the authors retrospectively analyzed previously collected data (ie, post hoc analysis), which could have influenced their results.

### DBS effect on mood

Like VNS, DBS has been used to treat psychiatric illnesses such as TRD and thus may have potential for improving mood in patients with epilepsy. In TRD, stimulation targets include subcallosal cingulate<sup>44</sup> or nucleus accumbens.<sup>45</sup> There is evidence though that DBS also positively affects mood in patients with epilepsy. Objective data from the SANTE trial showed that DBS on the ATN likely elevates mood as well as decreases seizure frequency.<sup>37</sup> At 5 years after implantation, patients had significant improvements in depression, tension/anxiety, and total mood disturbances when compared to baseline. Further analysis showed that Profile of Mood State (POMS) test scores for depression or apathy did not change significantly between baseline prior to implantation and 7 years postoperatively (Table 3).<sup>38</sup> The limitation of the current evidence is that the strongest data all come from the same study (ie, SANTE trial), which creates the need for additional investigation.

### Responsive neurostimulation

In contrast to VNS and DBS, which deliver "open-loop" (ie, scheduled intermittent or continuous) electrical stimulation to their targets, RNS is a "closed-loop" therapy that involves delivery of electrical stimulation directly to the seizure focus only in response to detection of abnormal pattern of neural activity.<sup>46</sup> RNS is indicated when a patient has multiple seizure foci (eg, bilateral mesial temporal onset) or when a seizure focus co-localizes with eloquent cortex.<sup>47,48</sup> The first multicenter, double-blind, randomized, controlled trial of 191 patients that assessed RNS efficacy came from the RNS System Pivotal Trial, which found that patients who underwent RNS treatment had a significantly higher seizure reduction than the sham control group.<sup>49</sup> Specifically, seizure reduction was 41.5% and 9.4% for the treatment and sham group, respectively, 5 months after implantation. Recently published long-term outcome data indicate that the median seizure reduction increased to 65.7% at approximately 6 years and that the responder rate was 59.1% (Table 1).<sup>50</sup> There were a number of complications associated with patients in the trial, including memory impairment endorsed by 8 patients (4.2%).<sup>49</sup> However, this was a subjective endorsement and preimplantation assessment showed that over 50% of patients had preexisting memory impairment. Depression was reported in 3.1% of subjects. The rates of serious adverse effects, including infection (4.2%) and hemorrhage (2.1%), were comparable to other neurosurgical procedures involving intracranial hardware implantation,<sup>51</sup> and there were no permanent neurological consequences.

### RNS effect on cognition

The exact effect of RNS on cognition is still unclear, but the current literature suggests that it has a positive long-term effect on cognition (Table 2). Initially, the RNS System Epilepsy Study Group published some cognitive data along

with their findings on seizure reduction.<sup>49</sup> The patients were assessed objectively with neuropsychological tests (ie, Rey Auditory Verbal Learning Test I–V and Brief Visuospatial Memory Test-Revised) at baseline and the end of the blind evaluation period, which was 1–2 years postoperatively. Despite some subjective data of patients endorsing memory impairment, there were no objective declines in any cognitive metrics, and there were significant improvements in verbal functioning, visuospatial abilities, and certain aspects of memory.

Additional objective cognitive data from the RNS System Pivotal Trial were analyzed and published separately from the studies focused on seizure reduction.<sup>52</sup> The results showed small but significant beneficial treatment effects on naming in patients with neocortical seizure onsets, and modest improvements in verbal learning for patients with mesial temporal seizure onsets. A major limitation of these findings is that all the data come from the same group of patients in the RNS System Pivotal Trial. Well-controlled replication is required to confirm or reject these findings.

### RNS effect on mood

The current evidence suggests that RNS does not have any negative effects on mood, although there is limited available evidence (Table 3). Meador et al<sup>53</sup> published data from the RNS System Pivotal Trial on quality of life and mood, showing that there was a significant improvement in mood for patients undergoing RNS treatment. Specifically, they tested patients with the BDI-II and POMS at baseline and at 1 year and 2 years follow-up. There were significant decreases in BDI-II scores of 15.2% and 17.9% at 1 and 2 years of follow-up, respectively. For POMS scores, there was an insignificant decrease of 17.1% between baseline and 1 year but a significant decrease of 20.8% at 2 years. The authors argue that this is an important finding because patients with refractory epilepsy are more likely to be suicidal than those who can be medically managed. Although the current evidence is promising, additional research is required to confirm the results.

## LESS INVASIVE FORMS OF NEUROSTIMULATION

### Trigeminal nerve stimulation

Recently, there has been some investigation into the effects of TNS on refractory epilepsy. TNS involves stimulating the superficial branch of the trigeminal nerve with an external pulse generator. TNS has been used to treat psychiatric disorders, such as TRD.<sup>54</sup> TNS has also been shown recently to reduce seizure frequency. A large double-blind multicenter randomized, controlled trial of 50 subjects with partial-onset seizures showed that the responder rate at 18 weeks was 40.5% compared with 15.6% for the control group.<sup>55</sup> However, a later published correction clarified that, although there was improvement within the active

treatment group alone, there was no significant difference in effect between the treatment and control groups and evidence of efficacy was therefore insufficient. Subsequently published long-term data for the study showed that responder rates at 1 year were 36.8% and 25% for the treatment and control group, respectively.<sup>56</sup>

There are few studies that directly investigate the effects of TNS on cognition or mood for patients with refractory epilepsy. There is some evidence that TNS could be effective in treating depression. Shiozawa et al<sup>57</sup> presented a study of 11 patients with major depressive disorder and found that there was a significant reduction in depressive symptoms after 10 sessions of TNS. However, the limitations were a small sample size, lack of control group, short follow-up, and the lack of a double-blind study design. In addition, these patients did not undergo continuous stimulation like those treated for epilepsy.

### Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (or rTMS) is a noninvasive therapy that involves using an electromagnetic coil to generate magnetic fields that influence electrical activity in targeted brain regions. Evidence for the efficacy of rTMS for seizure reduction is mixed. A small blinded randomized-controlled trial showed that seizure reduction was weak and transient.<sup>58</sup> Conversely, another double-blind randomized, controlled trial showed that rTMS significantly decreased seizure frequency in patients with refractory epilepsy and cortical development malformations.<sup>59</sup> However, a limitation of both studies is the small sample size, which should be considered when interpreting the results.

There is some evidence that TMS improves cognition in healthy patients. A study of 15 patients showed that patients exposed to TMS targeted to either frontal or parietal lobes prior to testing performed better on cognitive tests than when they were exposed to a sham treatment.<sup>60</sup> Higher TMS strength was associated with greater improvement in performance. There is also some evidence that rTMS improves cognition in patients with refractory epilepsy. Fregni et al<sup>59</sup> also investigated the cognitive effects of rTMS in their study and found improvement for all their metrics. They tested patients with 3 cognitive tests at baseline, immediately after treatment, and 2 weeks afterward. The treatment group scores were significantly higher than the control group scores in right-handed simple reaction time (10.8% vs 1.1%) and Stroop test (17.1% vs –2.7%). Differences between scores for the other tests were not significant.

There is evidence that rTMS has a positive effect on mood in patients with depression, but it is unclear whether rTMS has any effect on mood in patients with refractory epilepsy. A double-blind randomized-controlled study of 70 patients showed that rTMS provided short-term improvement in patients with recurrent depression.<sup>61</sup> Subjects were

tested with 2 depression scales, and scores were recorded at baseline and immediately after undergoing 10 TMS daily sessions over a 2-week period. Both depression scales decreased roughly 45% from baseline at the end of treatment. However, there are no studies specifically investigating whether rTMS influences mood in patients with refractory epilepsy.

### Transcranial direct current stimulation

tDCS is a noninvasive neurostimulation technique that involves constant, low current delivered to the brain area of interest via electrodes on the scalp. A prospective randomized, controlled trial of 19 patients with refractory epilepsy showed that tDCS reduced the number of epileptiform discharges when compared to a sham treatment.<sup>62</sup> The mean reduction of epileptiform discharges relative to baseline at 1 month after tDCS was significantly greater for the treatment group than for the control group (−64.3% vs −5.8%). There was also a nonsignificant trend in mean seizure frequency reduction between the 2 groups, with reduction of seizures in the treatment and control groups of 44.0% and 11.1%, respectively. The limitations of this study include the short follow-up period (1 month), small sample size, and subject heterogeneity, which could have affected the results due to potential outside confounding factors. Other studies provide more robust seizure reduction results. A randomized-controlled study of 29 patients showed that a single treatment of 18 total minutes of tDCS resulted in a 42.1% seizure reduction versus 17.0% reduction for the control group.<sup>63</sup>

The effect of tDCS on cognition and mood is unclear. An abstract of preliminary data described cognitive effects of a single-blinded randomized, controlled trial where patients underwent 5 consecutive days of 20-minute tDCS treatments.<sup>64</sup> The patients were tested at baseline and subsequently after treatment with immediate, 5-minute delay, or 20-minute delay recall tests, as well as a Symbol Digit Modalities Test and Stroop Color Word Test. There were no significant treatment-related changes for any metric, prompting the suggestion that long-term larger studies were required. Conversely, there is evidence that tDCS has antidepressive effects. Results of a study where patients with major depressive disorder underwent tDCS treatment for 10 sessions over a 2-week period showed a reduction of 40.4% in a standardized depression scale evaluated by a blinded rater.<sup>65</sup> However, there are no studies investigating the effect of tDCS on mood specifically in patients with refractory epilepsy.

## STUDY LIMITATIONS

There are number of limitations to consider. First, although there were a number of well-controlled studies included in this review, many of them had a primary focus of investigating the effect of neuromodulation on seizure

reduction, rather than cognitive or mood outcomes. Therefore, evaluating the quality of the studies in terms of possible confounding variables was challenging because cognition and mood effect metrics were not the primary outcome variables. Second, there were no consistent psychometric or cognitive outcome measures across studies that allowed for between-study comparisons or statistical analysis, highlighting a need for standardization and verification across studies. Third, a number of studies were single-arm (ie, without control), which did not allow for proper treatment evaluation, as the treatment group could not be assessed against a proper control group. Fourth, the most rigorous form of experimentation is where cognition and mood are tested between patients who have neuromodulation turned on versus off. Although some studies presented here did utilize that methodology, most were retrospective or one-armed case series without control groups. Therefore, future research should focus on applying the most rigorous methodologies to provide more reliable evidence. The outcomes in the literature should be interpreted within the context of the limitations.

## CONCLUSION

Neurostimulation can be an effective seizure-reduction treatment for patients with refractory epilepsy who are not candidates for resective surgery. Neurostimulation may also modulate cognition and mood, although it is challenging to disentangle primary effects from effects secondary to seizure reduction. Here we reviewed the current evidence for how different invasive and noninvasive neurostimulation therapies affect cognition and mood. Invasive techniques are moderately better studied than newer noninvasive techniques. Overall, current evidence indicates that the neurostimulation therapies reviewed here do not produce deterioration in cognition or mood, and there is some evidence that cognition and mood may improve with some invasive forms of neurostimulation. However, the available evidence was generally limited to studies with small sample sizes or methodology susceptible to confounding. Better designed studies (eg, randomized, controlled or experimental trials) measuring established, standardized psychometric parameters are necessary to fully characterize the effects of neurostimulation on cognition and mood and to elucidate the mechanisms underlying these effects.

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